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TITLE: The Effect of Hypotensive Resuscitation and Fluid Type on Mortality, Bleeding, Coagulation and Dysfunctional Inflammation in a Swine Grade V Liver Injury Model

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14. ABSTRACT
To determine the optimal fluid resuscitation and anesthetic regimen for swine undergoing uncontrolled hemorrhage. Methods: 1. 37 swine at 3 institutions underwent femur fracture, controlled hemorrhage, hypothermia and resuscitation with normal saline and Grade V liver injury followed by 30 minutes of hemorrhagic shock without resuscitation. Animals were then randomized to controls, shams, whole blood, 1:1 PRBC:FFP, FFP alone and Hextend. Physiologic measurements and coagulation assays were compared between the 3 institutions. 2. 40 swine were randomized to receive midazolam and buprenorphine with either 1-3% isoflurane or IV ketamine (TIVA). Animals underwent a Grade V liver injury followed by 30 minutes of uncontrolled hemorrhagic shock and LR resuscitation to achieve and maintain a MAP of 65mmHg. Physiologic and inflammatory parameters were compared between groups. Results: 1. There was excellent reproducibility in all parameters measured between the 3 centers. Resuscitation with 1:1 FFP:PRBCs and whole blood resulted in significantly lower end of study lactate levels. End of study coagulation parameters were similar in all groups except the Hextend group which was significantly more coagulopathic than the other groups. 2. Mortality was significantly higher in animals receiving TIVA. Dysfunctional inflammation was significantly greater in animals receiving TIVA.

15. SUBJECT TERMS
Uncontrolled hemorrhage, resuscitation, animal model, femur fracture coagulopathy, swine, TIVA, ketamine

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INTRODUCTION:

Exsanguination is the leading cause of death on the battlefield. Lifesaving interventions include arresting hemorrhage and initiating resuscitation. The ideal resuscitation of combat casualties has not been determined. The traditional goal of resuscitation has been to restore perfusion. There is increasing evidence to suggest early correction of coagulopathy improves mortality. Specific aim 1 of this work was designed to determine the physiologic outcome and the effects on coagulation of various blood transfusion strategies versus Hextend in a severe combat relevant multisystem injury model. This was performed at 3 institutions to insure the results were reproducible. To our knowledge this is the first prospective, randomized animal model to be performed at multiple institutions concurrently.

In addition to fluid resuscitation, anesthetics play a critical role in the outcome of trauma victims. The ideal anesthetic would be east to administer, have minimal hemodynamic effects and minimal long term effects. We have previously shown that the use of a ketamine based total IV anesthetic (TIVA) results in improved hemodynamic outcomes and reduced dysfunctional inflammation. In our prior study, isoflurane was used as an induction agent for all animals in the study and the animals were resuscitated with a fixed volume of fluid. Furthermore, the study was only continued for 2 hours post-injury which may not be long enough to adequately evaluate the inflammatory effects of the differing anesthetic regimens. Specific aim 2 of this work was designed to determine if our previous results would be reproduced if TIVA was used as the sole anesthetic and animals were resuscitated to 65 mmHg consistent with hypotensive resuscitation.

BODY:

Materials and Methods

Specific Aim 3 – Hemostatic Resuscitation in a Multi-system Combat Relevant Model

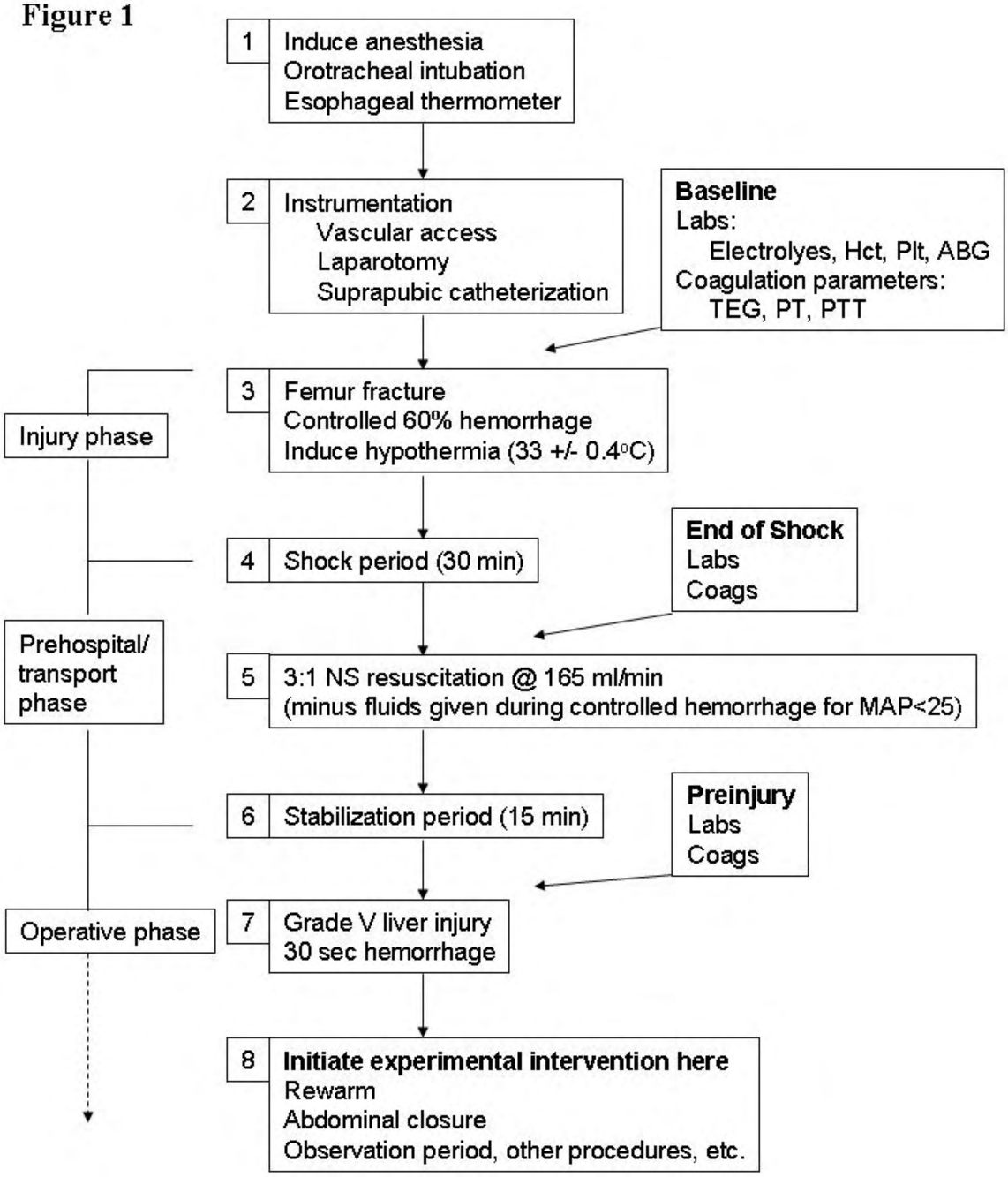
The model was developed at the Oregon Health and Science University, Portland, Oregon (center 1), and exported to the United States Army Institute of Surgical Research (USAISR, center 2) and Massachusetts General Hospital/Harvard Medical School (MGH, center 3).

We developed a complex, combat-relevant, multisystem injury model of liver injury, long bone fracture and soft tissue injury, and hemorrhagic shock with hypothermia and acidosis. We then simulated an injury phase, a preoperative phase (including prehospital care, transport and emergency department), and an operative phase of resuscitation. (Figure 1)

Study protocol

Thirty-seven female Yorkshire crossbred swine were utilized. Animals were delivered 7-10 days prior to the experiment in order to minimize the stress of transport and subsequent potential changes in sympathetic output or inflammatory mediators. An overnight fasting period was observed with the exception of water ad libitum. All animals were ordered such that their weight at the time of the experiment was 39.7 ± 1.1 kg (mean ± SEM). No attempt was made to use a

Figure 1



single vendor, and each center made their own arrangements for procurement of animals according to their standard sources.

Anesthesia

Anesthesia was induced with 8 mg/kg Telazol® (tiletamine hydrochloride 50 mg/ml, zolazepam hydrochloride 50 mg/ml, Fort Dodge Animal Health, Fort Dodge, Iowa) intramuscularly and isoflurane at 1-3% inhaled. Orotracheal intubation was performed after which an esophageal thermometer was placed. Throughout the study anesthesia was maintained to the clinical endpoints of reflexes and muscle relaxation as is done in humans.

Monitoring, access and pre-experiment procedures

Vascular access was established via neck cutdown and placement of carotid artery and external and internal jugular vein catheters. The femoral artery was cannulated for blood pressure monitoring. Baseline labs were collected and included electrolytes, lactate, spun hematocrit (Hct), activated clotting time (ACT), platelets (Plt), prothrombin time (PT), partial thromboplastin time (PTT), and arterial blood gas (ABG). In addition, a baseline thrombelastogram (TEG, Haemoscope Corporation, Niles, IL) was performed. A celiotomy was then performed, at which time a suprapubic bladder catheter was placed to monitor urine output.

Injury phase

After needle localization, a captive bolt gun was used to fracture the femur and create a soft tissue injury at the midshaft of the left femur. Figure 2 is a 3-D computed tomography (CT) reconstruction of a typical femur fracture created in a study animal by these methods. A controlled hemorrhage was then initiated to remove 60% of the blood volume based on a published, standard equation relating blood volume to body weight for domestic swine. During this period if the mean arterial blood pressure (MAP) fell below 25mm/Hg, normal saline (NS) was infused at a rate of 165 ml/min to keep the MAP>25 mm/Hg. The animal was then cooled to 33 +/-0.4^{o}C using cooled intraperitoneal lavage with crystalloid as needed (most of the animals developed a degree of hypothermia spontaneously due to shock and infusion of IV fluids). These procedures were followed by a 30-minute shock period, representing time in the field prior to medical intervention.

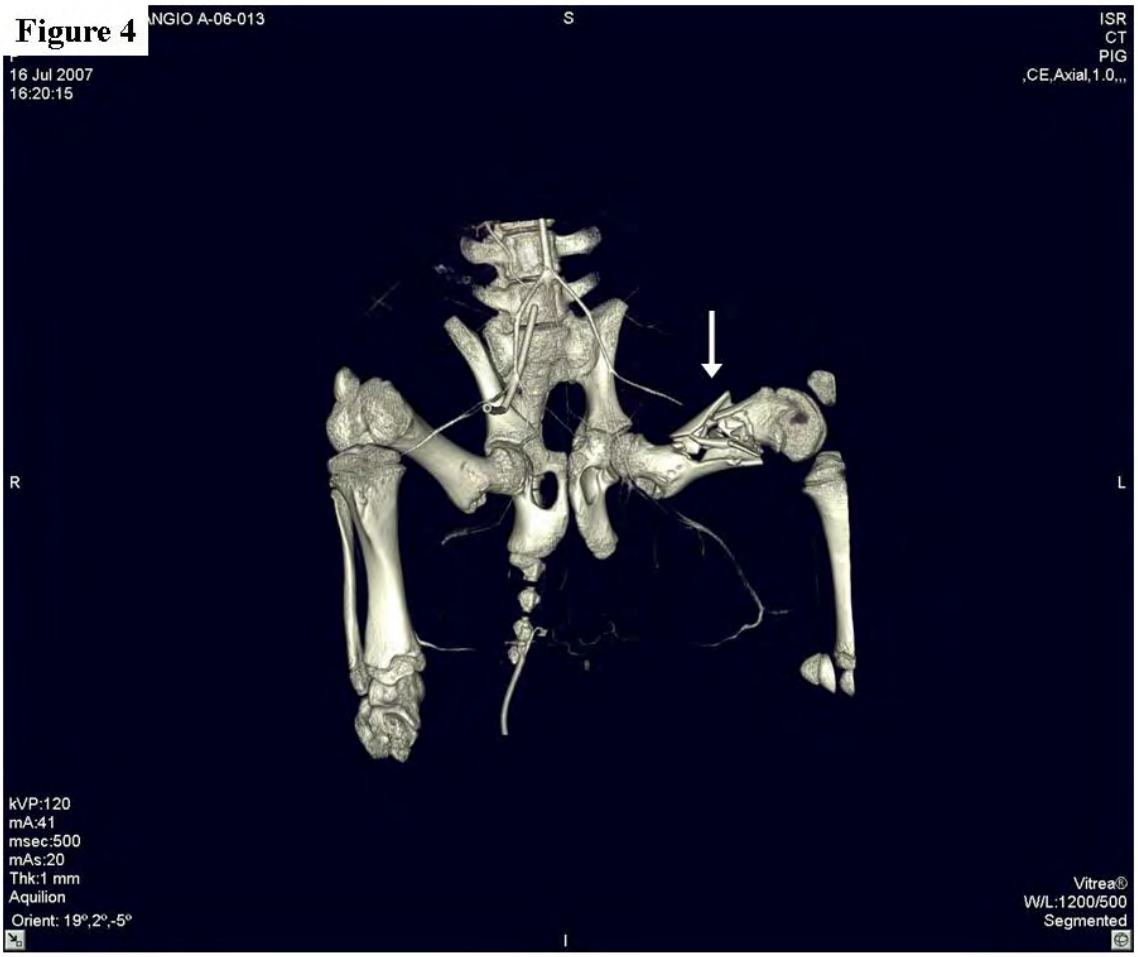
Prehospital care/transport phase

After the 30-minute shock period, electrolytes, spun hematocrit, ACT, PT, PTT, platelets, ABG, and TEG were again recorded. After coagulation studies and lab collection, the hemorrhage volume was replaced with a 3:1 ratio of NS infused at a rate of 165 ml/min, minus any given during the controlled hemorrhage. This reflects current civilian prehospital resuscitative practices.

Operative phase

Following NS resuscitation, a 15-minute stabilization period was observed, during which a baseline MAP was recorded and preweighed laparotomy sponges were placed in both paracolic gutters and in the pelvis for blood collection. Labs and coagulation studies were again collected, and a previously described grade V liver injury was created at the confluence of the right and

Figure 2. CT scan showing extent of the femur fracture. The arrow points to the fractured left femur.



middle hepatic veins using a specialized clamp. Thirty seconds of hemorrhage were then followed by evacuation of blood from the abdomen and packing of the liver with a fixed number of additional preweighed laparotomy sponges. The liver injury was designed to provide a second stressor after initial injury and also to create a standardized injury that had the potential to rebleed, both of which simulate a laparotomy after trauma in a patient with solid organ injury. Thirty seconds after injury, the liver was packed with laparotomy sponges in a standardized fashion. Randomized treatments were initiated at the same time as packing was initiated. Randomization groups included controls (no resuscitation), whole blood, 1:1 FFP:PRBCs, FFP and Hextend. A sham group underwent all surgical procedures to include femur fracture, exploratory laparotomy and line placement but did not undergo controlled hemorrhage, liver injury or resuscitation. The volume of the treatment resuscitation was equivalent to the blood loss from the controlled hemorrhage.

Study Variables

Physiologic variables included survival, MAP, blood loss from the controlled hemorrhage, and blood loss due to the liver injury. Laboratory values include Hct, lactate, Plt, ABG, and electrolytes. Coagulation parameters include the PT, PTT, ACT, and TEG values.

Statistical Analysis

Mean values of study variables between centers were compared using a one-way analysis of variance (ANOVA). We assumed that our study populations were normally distributed and that the variances of the populations were equal. A post-hoc Bonferroni correction was applied to account for multiple comparisons. The significance level was set at a p value of less than 0.05. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

Specific Aim 7 – Comparison of the effects of Isoflurane anesthesia and TIVA anesthesia on systemic inflammation and local mRNA production in the lung.

This was a randomized controlled trial using forty female Yorkshire crossbred swine. The animals were fasted for 16 hours prior to surgery, except for water ad libitum. We pre-anesthetized the swine with an intramuscular injection of 8mg/kg Telazol® (Fort Dodge Animal Health, Fort Dodge, Iowa). All animals received midazolam (1-2 mg/kg) and buprenorphine (2-10 mg/kg) as needed to maintain adequate anesthesia. Animals randomized to receive ISO also received isoflurane for induction and animals that randomized to TIVA received a ketamine infusion during induction. Orotracheal intubation was performed with a 7.0mm or 7.5mm internal diameter cuffed endotracheal tube, and the animals were placed on mechanical ventilation. Respiratory rate and tidal volume were adjusted to keep pCO2 values between 40-50 torr. An esophageal thermometer was placed, and the animal temperature was maintained at 38.0 ± 1.5°C using external warming devices. A bispectral index monitor (BIS) was placed on the animals' head to monitor the level of anesthesia.

Eight swine (4 ISO and 4 TIVA) were randomized to a control arm and underwent sacrifice and tissue harvesting after induction of anesthesia. Cytokine mRNA levels from these animals served as baseline data for the population. Twelve animals (6 ISO and 6 TIVA) randomized to a sham group that underwent celiotomy, splenectomy and 4 hours of anesthesia.

Following induction, an 18 gauge aural intravenous (IV) catheter was placed. Animals were then switched to the blindly randomized (using a random numbers table) maintenance anesthesia consisting of either 1-3% ISO, or TIVA consisting of IV ketamine (15-33mg/kg/hr). These doses fall within the normal, therapeutic range for swine. The ISO group received an equivalent volume of lactated Ringer's solution (LR) instead of the IV medications to standardize the volume of fluid administered. The level of sedation was constantly monitored by an animal technician independent of the study team through measurement of jaw laxity, hemodynamic fluxuations, and response to painful stimuli at the nasal septum and forefoot. All efforts were made to ensure the study team remained blinded to the anesthetic regimen.

A left ventral cervical cut down was performed and 8F polyethylene catheters were inserted into the common carotid artery, external jugular vein, and internal jugular vein. The

arterial catheter was used for continuous blood pressure analysis and blood sampling. Mean arterial pressure (MAP), and heart rate (HR) were continuously recorded and averaged every 10 seconds using a digital data collection system with a blood pressure analyzer (DigiMed, Louisville, Kentucky). The external jugular catheter was used for fluid resuscitation. The infusion of either the TIVA medications or LR (in the ISO group) was switched from the aural catheter to the internal jugular vein catheter upon its placement.

The animals underwent a midline celiotomy, suprapubic Foley catheter placement, and splenectomy. Splenectomies are performed in swine hemorrhage studies because the swine spleen in distensible and contains highly variable amounts of blood that can act as an auto-transfusion. The spleen was weighed and LR was infused to replace three times the spleen weight in grams. The abdomen was then closed with towel clamps.

Following a 15-minute stabilization period, the blood pressure was recorded and used as the baseline MAP. The abdomen was opened and residual peritoneal fluid was removed. Pre-weighed laparotomy pads were placed in both paracolic gutters and the pelvis to facilitate blood collection. A standardized Grade V liver injury (injury to a central hepatic vein) was created using a specially designed clamp. The clamp was positioned in the middle of the liver, placing the right hepatic vein, left hepatic vein, and portal vein at risk for injury. This protocol is based upon our previous studies of uncontrolled hemorrhagic shock using this same model. The time of injury was considered the start of the study (time point 0). During hemorrhage, the anesthetic regimen was stopped when the MAP was below 30 mmHg, and restarted upon rising above 30mmHg for both groups. Following 30 minutes of uncontrolled hemorrhage, the initial blood loss was determined using wall suction and the pre-weighed laparotomy pads. The abdomen was then closed. LR was given at 165ml/min to achieve and maintain a MAP of 65 mmHG. The rate of administration is approximately one half the rate delivered by the Level 1 rapid infuser® as the animals were approximately one half the weight of an average human.

Upon completion of the 4-hour study period, the abdomen was reopened and the secondary blood loss was determined by adding the volume of intra-abdominal blood and the weight of the intra-abdominal blood clots. Following completion of the study the animals were sacrificed and lung tissues harvested. To ensure comparable injuries between study groups, we removed the liver post-mortem and analyzed the number of hepatic vessels injured.

Blood specimens were collected at baseline and every 60 minutes until completion of the 4-hour study. Blood assays included lactate, arterial blood gas, chemistry panel, liver function tests, and hematocrit. Serum for cytokine analysis was collected at baseline and at study completion. Lung tissues harvested were immediately placed in RNA*later*™ solution (Ambion, Autsin, Texas) and stored at -80°C.

Serum and Tissue Cytokine Analysis

Serum cytokine levels were quantified using the Quantikine® enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN). Lung tissue levels of IL-6, IL-8, and TNF-α mRNA were determined using the technique of quantitative, real-time reverse transcriptase polymerase chain reaction (RT-PCR). β-actin was used as an endogenous control. Total RNA was isolated from RNA*later*™-stored lung tissue using a commercially available kit (RNeasy® Mini Kit; Qiagen, Valencia, CA). The extracted RNA concentration was determined with a spectrophotometer based on the absorbance at 260nm. Two micrograms of RNA was reverse-trascribed into cDNA using the SuperScript™ III First-Strand Synthesis System for RT-PCR (Invitrogen, Carlsbad, CA) using random hexamers, according to the package protocol.

Twenty-five nanograms of cDNA was used for performing quantitative RT-PCR using the Applied Biosystems 7900HT (Applied Biosystems; Foster City, CA) under the following conditions: Stage 1) 2 minutes at 50°C, Stage 2) 10 minutes at 95°C, Stage 3) 40 cycles of 15 seconds of melting at 95°C followed by DNA synthesis for 1 minute at 60°C.

Primers and probes used for specific PCR amplification and quantification of swine β-actin, IL-6, IL-8, and TNF-α mRNA were derived from published swine sequences.[33-36] Primers and probes were created (using the Assays-by-Design software from Applied Biosystems) to bind at unique, and individualized sites on the gene of interest to reduce interference. Primers and probes were used at concentrations of 18μM, and 5μM, respectively. The primer and probe sequences are as follows, each from 5' to 3':
β-actin forward primer: TCTTCCAGCCCTCCTTCCT, β-actin reverse primer: TCGCACTTCATGATGGAGTTGA, β-actin probe: [FAM]-CCTGCGGCATCCAC-[NFQ];
IL-6 forward primer: TGCTTCCAATCTGGGTTCAATCAG, IL-6 reverse primer: GCTCTCATACTCTTTCTGGAGGTAGT, IL-6 probe: [FAM]-TCACCACCGGTCTTGTG-[NFQ]
IL-8 forward primer: CTGGCAAGAGTAAGTGCAGAACT, IL-8 reverse primer: GTCCACTCTCAATCACTCTCAGTT, IL-8 probe: [FAM]-CCAGTGCATAAATACG-[NFQ]
TNF-α forward primer: CAGATCATCGTCTCAAACCTCAGAT, TNF-α reverse primer: TCCCTCGGCTTTGACATTGG, TNF-α probe: [FAM]-CCGTCGCCCACGTTGT-[NFQ]

(NFQ = Non-Fluorescent Quencher)

Statistical Analysis

An independent samples *t* test was used to compare the means of continuous variables between the two groups. Fisher's exact test was utilized when the n for a given data set was less than 5. Statistical significance was defined as a *p* value <0.05. Values within a group and comparisons of three or more groups were compared using a posthoc analysis of the variance (ANOVA). These values were calculated using SPSS version 15.0 software (SPSS Inc., Chicago, IL).

RESULTS

Specific Aim 3

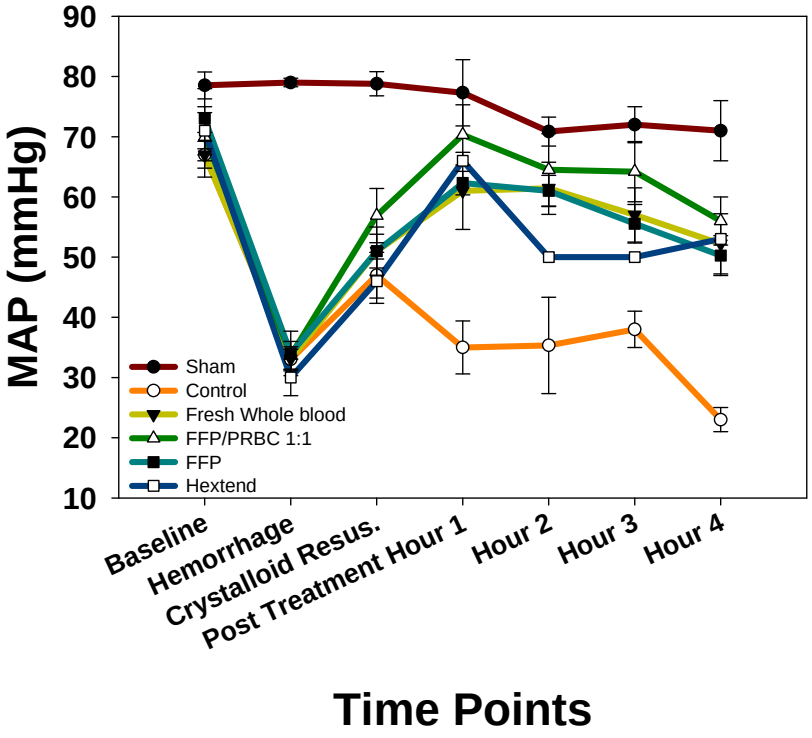
Eight of the animals died during the model period, for a mortality rate of 21.6%. Animals that died prior to the completion of the model period (liver injury and 30-second blood loss) were excluded from the analysis in that all data points could not be collected. Mortality was 85% in the control group, 80% in the Hextend group and 0% in each of the blood component groups ($p < 0.05$).

Physiologic variables

Hypothermia was achieved during the shock period, with a pre-liver injury temperature of 33.1 ±0.07^{o}C. Blood loss from the controlled hemorrhage, a function of the calculated blood volume, was 1708 ±35.6 ml or 43.2 ± 0.3 ml/kg body weight.

Mean arterial pressures across groups are shown in Figure 3. Prior to randomization of care animals in all injury groups had a similar physiologic profile with an acute drop in blood pressure, followed by autoresuscitation. MAPs did not differ significantly between surviving animals in the injury groups at the end of the study. Standard error bars reveal minimal variation between centers.

Figure 3.



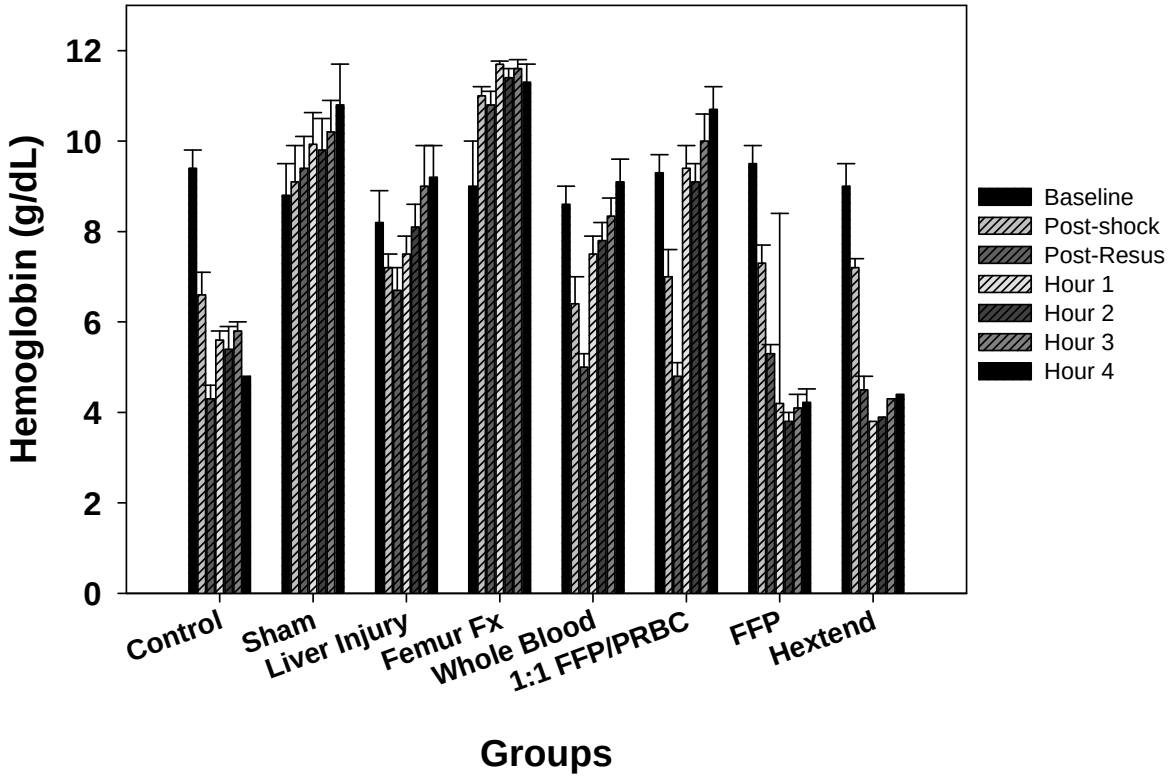
Laboratory variables

Baseline, end of shock, and pre-injury hemoglobin values were similar between centers ($p>0.10$). A significant decrease in Hgb was seen over the three study phases. The change in Hgb between baseline and end of shock was significant ($p<0.0001$), as was the change in Hgb from the end of shock to pre-injury ($p<0.0001$). Animals in the Hextend and FFP groups had significantly lower Hgb levels at the end of the study compared to animals in the 1:1 group and the whole blood gropup. Figure 4 illustrates these results.

Lactate and base deficit (BD) were different among the three centers at the baseline and end of shock periods. By pre-liver injury, after resuscitation with NS, all BD and lactate values were similar among the three centers. At pre-injury, mean overall BD was 8.2 ±0.65 mEq/L and the mean overall lactate was 5.3 ±0.44 mmol/L. The BD increased at each specific center between baseline and pre-injury ($p<0.0001$). Lactate values increased at each center from baseline to pre-

injury ($p<0.0001$). At the end of the study, lactate levels were significantly higher in animals receiving FFP and Hextend. Figure 5 illustrates these results.

Figure 4. Hemoglobin levels throughout the study



Coagulation parameters

Prothrombin times in all groups increased significantly after normal saline resuscitation confirming that coagulopathy was produced by the model. Following treatment, PT values were reduced toward baseline in each of the blood transfusion groups. The PT was significantly increased after treatment with Hextend ($p < 0.01$). The standard error of the mean for these values was very small indicating excellent reproducibility between centers. (Figure 6)

Figure 5. Lactate levels.

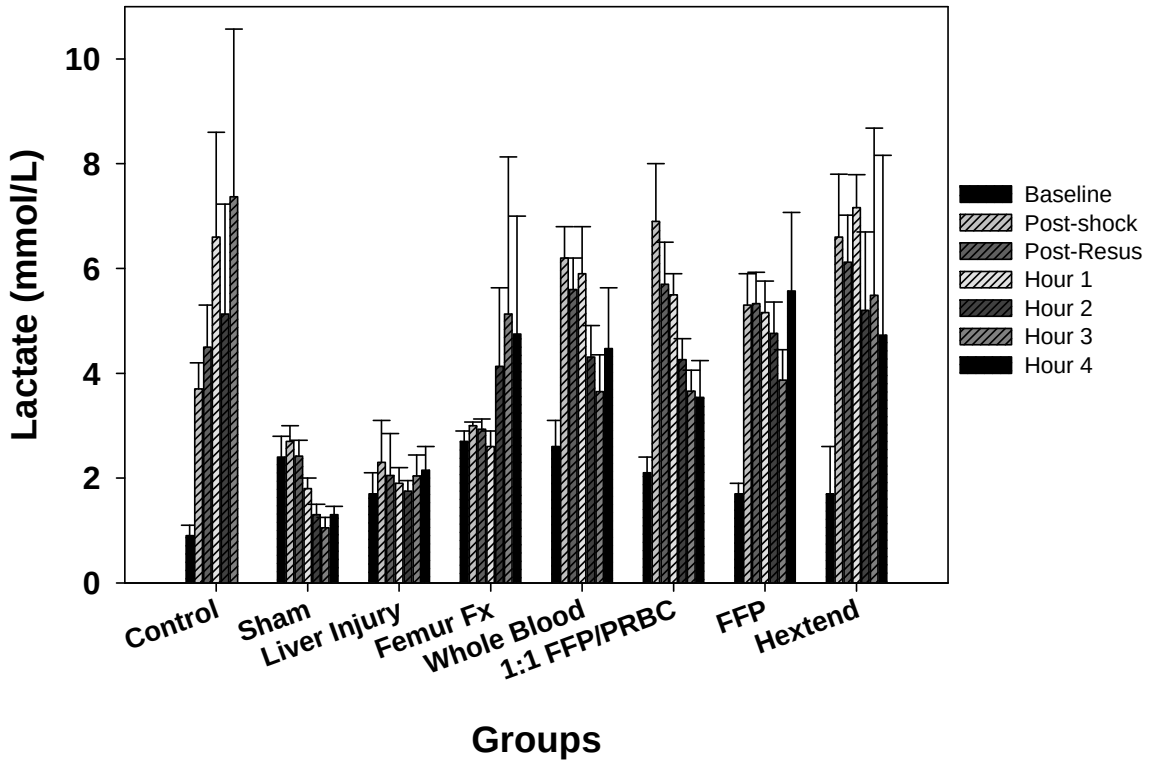
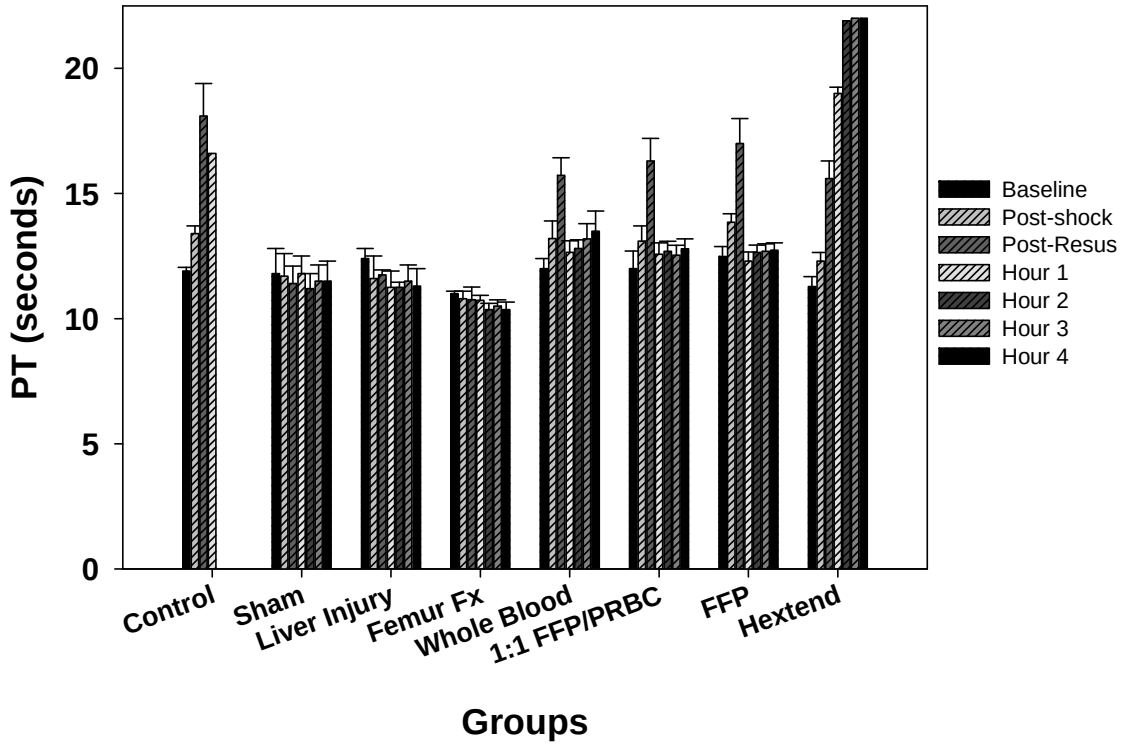


Figure 6. Prothrombin Time Values



Specific Aim 7.

Animal weight and injury pattern were similar between the animals in the uncontrolled hemorrhage groups. There was no difference in estimated blood loss (EBL), resuscitation volume or urine output between groups. More animals in the ketamine/injury arm died prematurely (5 of 10) than in the isoflurane/injury arm (0 of 10) ($p = 0.03$). The five animals that died prematurely had a significantly higher blood loss ($p < 0.001$). There was no difference in blood loss between the surviving ketamine/injury animals and the isoflurane/injury animals.

There was no difference in the pre- or post-injury mean arterial pressures, heart rate or peripheral oxygenation between groups. Mean arterial pressures are compared between groups in Figure 1. As shown in the figure, animals that died in the ketamine group had a lower MAP at baseline and they died very quickly after injury.

There was no difference in lactate values or base deficit between groups. (Figure 2) Animals receiving ketamine had a significantly higher BIS score ($p < 0.01$) and a higher serum sodium level ($p < 0.05$) at baseline, after injury and after resuscitation.

Serum cytokines levels, measured at the end of the study, are shown in figure 3. There was no difference in levels for IL-6. IL-8 and TNF-a levels were significantly greater in animals receiving TIVA than those receiving ISO. Lung tissue cytokine mRNA fold changes are shown in figure 4. Fold change of controls is defined as 1. Fold change was greater for TNF-a in the TIVA group but not different for the other 2 cytokines.

Table 1.

	Ketamine (n=10)	**ISO (n=10)**	**p**
Weight	36.23 ± 4.6 kg	35.38 ± 2.8 kg	0.63
Survival	5	10	0.03
EBL after injury (ml)	987.9 ± 315.5	1047.4 ± 267.5	0.71
EBL per kg per min alive (ml)	0.16 ± 0.05 (alive) (3.02 ± 3.06 [dead])	0.18 ± 0.05	0.28 (> 0.10)
Resuscitation volume (ml)	5588 ± 3300	6990 ± 4137	0.52
Total UOP (ml)	520.0 ± 445.6	389.0 ± 285.4	0.50
Total UOP per kg (ml)	14.6 ± 13.5	10.8 ± 7.3	0.49

Figure 1.

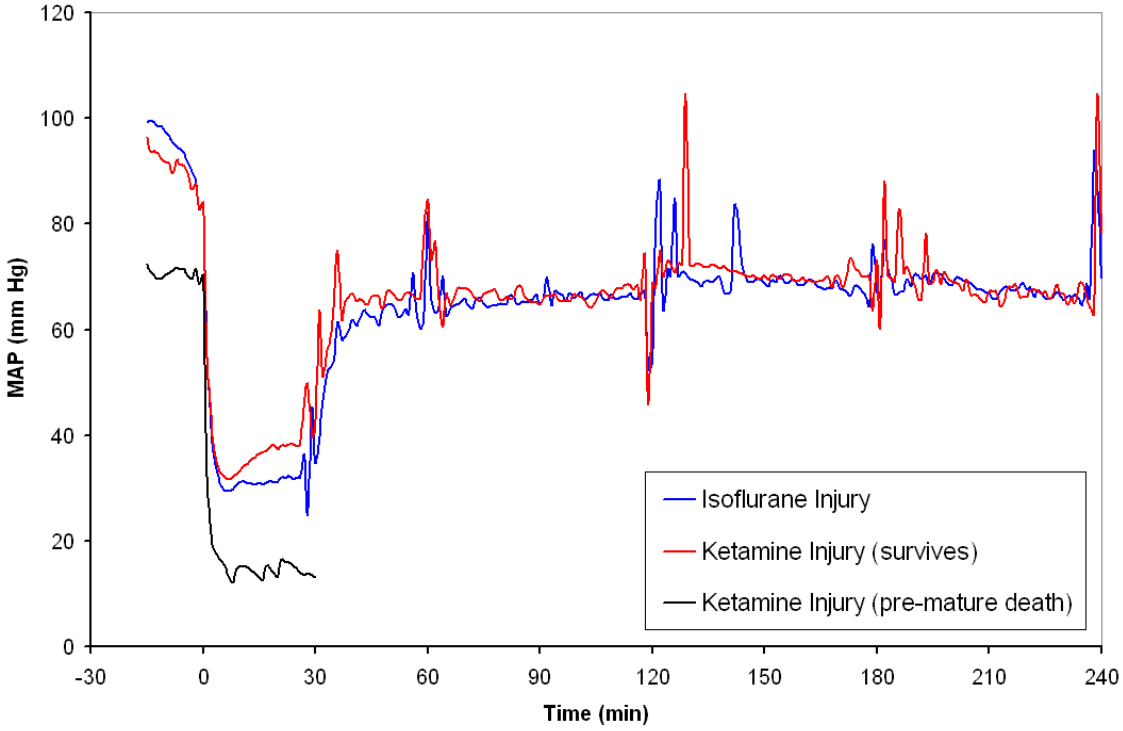


Figure 2. Lactate compared between groups

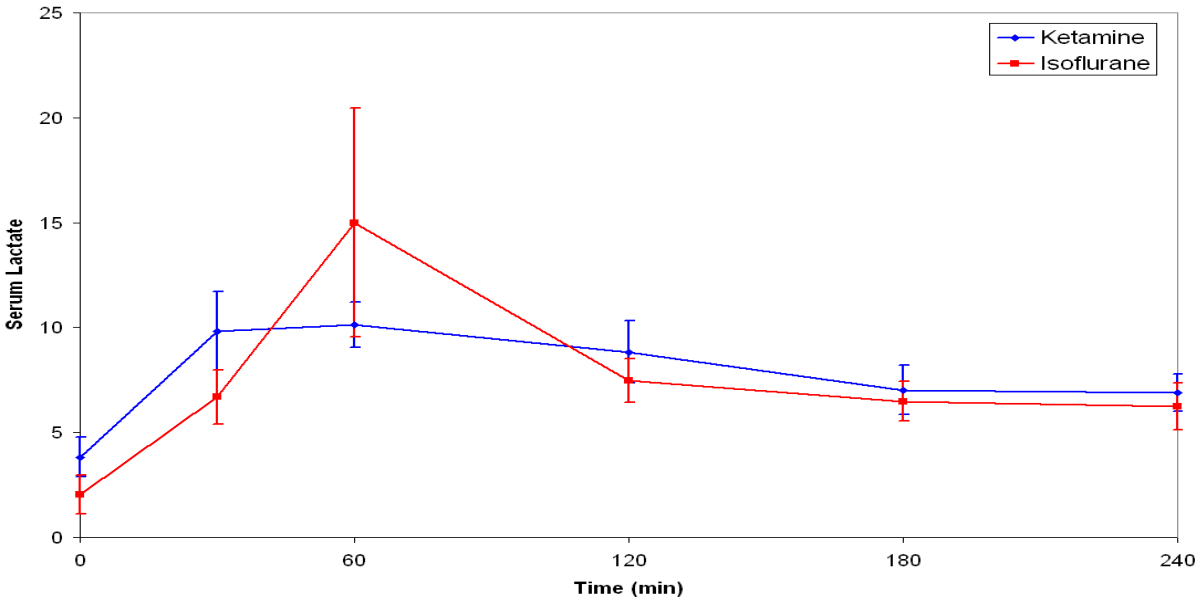


Figure 3. Serum cytokine levels.

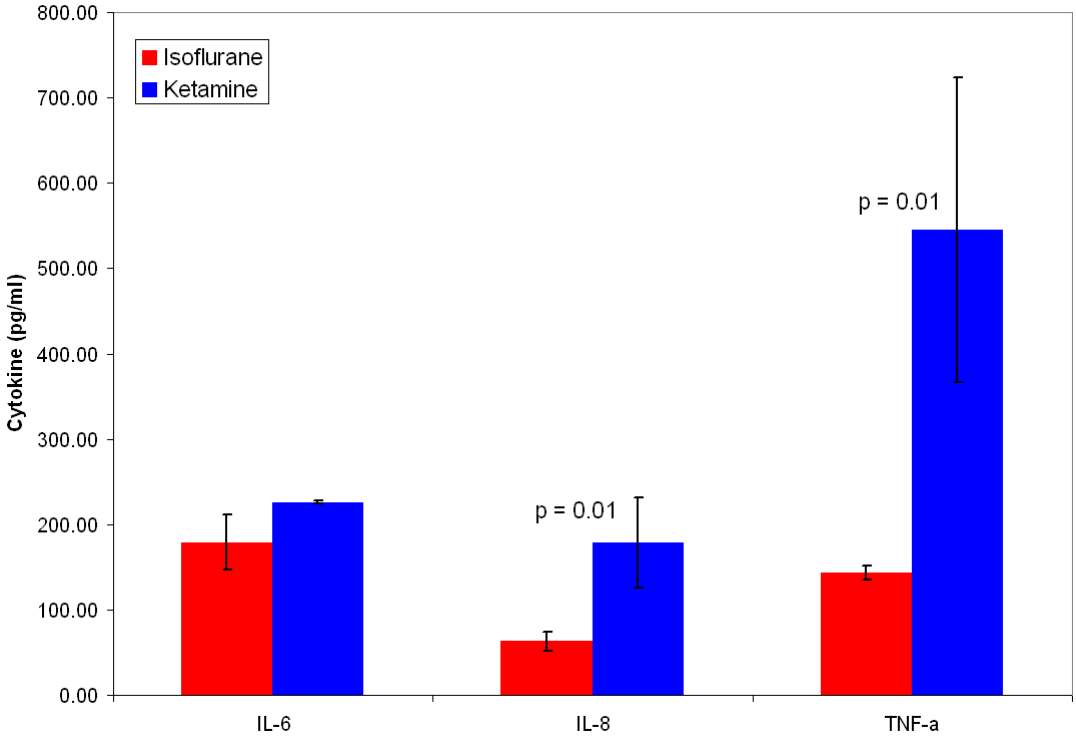
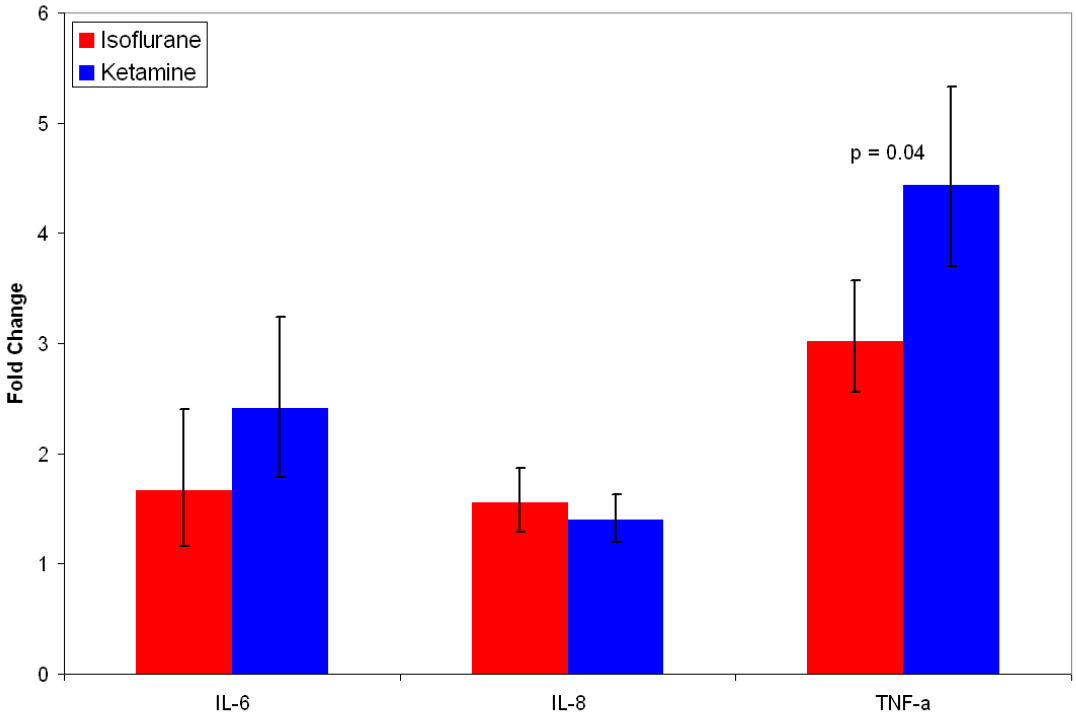


Figure 4. Lung tissue cytokine mRNA fold change.



KEY RESEARCH ACCOMPLISHMENTS

1. A severe multi-system combat relevant shock model can be reproduced at multiple centers.
2. Use of Hextend in a severe multi-system model increases mortality compared to blood products including fresh frozen plasma in the absence of red blood cells.
3. Resuscitation with fresh whole blood and 1:1 PRBCs:FFP results in similar hemodynamic and physiologic outcomes.
4. Resuscitation with fresh whole blood, FFP and 1:1 PRBCs:FFP results in similar mortality and similar end of study coagulation parameters.
5. The exclusive use of TIVA results in increased mortality compared to isoflurane in a Grade V liver injury model in swine.
6. The exclusive use of TIVA results in increased dysfunctional inflammation measured in serum cytokines measured at 4 hours after injury.
7. The exclusive use of TIVA results in increased dysfunctional inflammation measured in lung tissue.

REPORTABLE OUTCOMES

Specific Aim 3 was presented at the 2007 ATACCC meeting and the 2007 Shock Society meeting. This work was also presented the 2007 Region X Residents' Competition of the American College of Surgeons Committee on Trauma. The manuscript has been submitted for publication in the journal Shock.

Specific Aim 7 was presented at the 2007 Region X Residents' Competition of the American College of Surgeons Committee on Trauma. The work is also scheduled to be presented at the 2007 combined meeting of the Association of Academic Surgeons and the Society of University Surgeons.

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ABSTRACTS

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